β_2-Agonist Therapy in Lung Disease

Mario Cazzola[1,2], Clive P. Page[3], Paola Rogliani[1], and M. Gabriella Matera[4]

[1]Department of System Medicine, University of Rome Tor Vergata, Rome, Italy; [2]Department of Pulmonary Rehabilitation, San Raffaele Pisana Hospital, IRCCS, Rome, Italy; [3]Sackler Institute of Pulmonary Pharmacology, Institute of Pharmaceutical Science, King's College London, London, United Kingdom; and [4]Department of Experimental Medicine, Second University of Naples, Naples, Italy

β_2-Agonists are effective bronchodilators due primarily to their ability to relax airway smooth muscle (ASM). They exert their effects via their binding to the active site of β_2-adrenoceptors on ASM, which triggers a signaling cascade that results in a number of events, all of which contribute to relaxation of ASM. There are some differences between β_2-agonists. Traditional inhaled short-acting β_2-agonists albuterol, fenoterol, and terbutaline provide rapid as-needed symptom relief and short-term prophylactic protection against bronchoconstriction induced by exercise or other stimuli. The twice-daily β_2-agonists formoterol and salmeterol represent important advances. Their effective bronchodilating properties and long-term improvement in lung function offer considerable clinical benefits to patients. More recently, a newer β_2-agonist (indacaterol) with a longer pharmacodynamic half-life has been discovered, with the hopes of achieving once-daily dosing. In general, β_2-agonists have an acceptable safety profile, although there is still controversy as to whether long-acting β_2-agonists may increase the risk of asthma mortality. In any case, they can induce adverse effects, such as increased heart rate, palpitations, transient decrease in Pa_{O_2}, and tremor. Desensitization of β_2-adrenoceptors that occurs during the first few days of regular use of β_2-agonist treatment may account for the commonly observed resolution of the majority of these adverse events after the first few doses. Nevertheless, it can also induce tolerance to bronchoprotective effects of β_2-agonists and has the potential to reduce bronchodilator sensitivity to them. Some novel once-daily β_2-agonists (olodaterol, vilanterol, abediterol) are under development, mainly in combination with an inhaled corticosteroid or a long-acting antimuscarinic agent.

Keywords: β_2-agonists; pharmacology; asthma; COPD; guidelines

Yamanashi and colleagues isolated ephedrine, a nonselective α-adrenoceptor (AR) and β-AR agonist, in 1887 from the Chinese herb ma huang, which has been used for over 5,000 years to treat asthma, hay fever, and bronchitis (1). At the beginning of the twentieth century, epinephrine was introduced into clinical practice and was administered by the subcutaneous route for the treatment of acute asthma. However, the history of β_2-agonists really started with the discovery of albuterol by Sir David Jack and colleagues (1). The early β_2-agonists, albuterol, fenoterol, and terbutaline, have a short duration of action, typically 4 to 6 hours, and are referred to as short-acting β_2-agonists (SABAs). Consequently, the next advance was the development of the longer-acting agents salmeterol and formoterol, referred to as long-acting β_2-agonists (LABAs), whose duration of action is approximately 12 hours, which made their use more appealing (1). More recently, several newer β_2-agonists with longer pharmacodynamic half-lives have been discovered and called ultra-LABAs, of which indacaterol is the archetype and already marketed as a once-daily treatment (2).

MECHANISM OF ACTION

β_2-Agonists are effective bronchodilators due primarily to their ability to relax airway smooth muscle (ASM). They exert their effects via their binding to the active site of β_2-ARs, which are densely located on ASM. The presumed cellular mechanism of action involves the canonical signaling pathway via activation of adenylyl cyclase (AC) and generation of intracellular cAMP, which in turn can activate the effector molecules cAMP-dependent protein kinase A (PKA) and Epac, a Rap1 guanine nucleotide exchange factor (3) (Figure 1). PKA phosphorylates key regulatory proteins involved in the control of ASM tone, Epac induces ASM relaxation in a largely PKA-independent manner through down-regulation of Rho, and cAMP results in sequestration of intracellular Ca^{2+}, leading to relaxation of the ASM (4). However, it has become increasingly clear that signaling through adenylyl cyclase–coupled pathways is considerably more complex and sophisticated than was previously considered, although there is still little known regarding these pathways in airway cells (4).

PHARMACOKINETICS

When β_2-agonists are administered by inhalation, a route that enables delivery of low doses of an aerosolized drug to its site of action for a localized effect and, consequently, a rapid clinical response with less systemic side effects, the therapeutic effects depend on local tissue concentrations that may not be directly related to plasma drug concentrations. In fact, the peak plasma β_2-agonist concentration is able to account for only a small fraction of the decrease in airway resistance (5), and even though very little of the inhaled dose of a β_2-agonist reaches the airways, this small amount produces effective bronchodilatation (5).

β_2-Agonists are eliminated via the systemic circulation. Systemic drug concentrations will in general result from absorption of drug across the pulmonary vascular bed and also via the gastrointestinal tract; a portion of an inhaled drug is always swallowed through the oropharynx and can thus reach the systemic circulation from the gastrointestinal tract (5). Systemic absorption of the drug can cause unwanted side effects.

PHARMACODYNAMICS

β_2-Agonists act by mimicking some of the effects of epinephrine at several levels: (*1*) inhibitory action on ASM; (*2*) stimulation of the heart, leading to increased heart rate, contraction, and conduction; (*3*) inhibition of the release of mediators from mast cells; (*4*) metabolic actions (e.g., glycogenolysis in liver and skeletal muscle, resulting in an increase in glucose); (*5*) endocrine actions (increasing insulin and glucagon release); and (*6*) prejunctional

(*Received in original form September 26, 2012; accepted in final form January 10, 2013*)

Correspondence and requests for reprints should be addressed to Mario Cazzola, M.D., Dipartimento di Medicina dei Sistemi, Università di Roma Tor Vergata, Via Montpellier 1, 00133 Rome, Italy. E-mail: mario.cazzola@uniroma2.it

Am J Respir Crit Care Med Vol 187, Iss. 7, pp 690–696, Apr 1, 2013

Originally Published in Press as DOI: 10.1164/rccm.201209-1739PP on January 24, 2013
Internet address: www.atsjournals.org

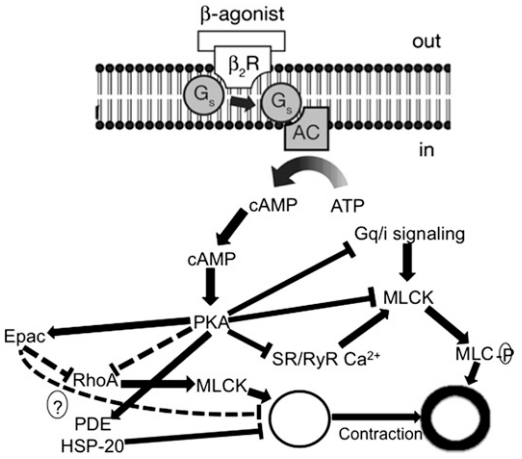

Figure 1. Mechanism of action of β_2-agonists (based on information from Reference 3). AC = adenylyl cyclase; β_2R = β_2 receptor; cAMP = cyclic adenosine monophosphate; Epac = exchange protein directly activated by cAMP; G_s = stimulatory G-protein; HSP-20 = heat shock–related protein 20; MLCK = myosin light chain kinase; MLC-P = myosin light chain phosphatase; PDE = phosphodiesterase; PKA = protein kinase A; SR/RyR Ca^{2+} = sarcoplasmic reticular ryanodine Ca^{2+} channel.

action on parasympathetic ganglia, increasing or decreasing acetylcholine release (1). In addition to their main bronchodilator effect, this class of drugs also protects against the actions of bronchoconstrictor stimuli.

CLINICAL USE

SABAs are currently only used as rescue medications for obstructive lung diseases, because their short half-life limits their use as maintenance treatments. On the contrary, LABAs and ultra-LABAs provide sustained bronchodilation and, although they are unable to influence the accelerated decline in lung function characteristic of chronic obstructive pulmonary disease (COPD), at least in terms of clinically noticeable changes, they offer greater convenience for patients with COPD. Actually, they induce significant improvements in FEV_1, reduce dynamic hyperinflation, and improve exercise tolerance (1, 2), causing improvements in dyspnea and health-related quality of life (HRQoL) (1, 2). Moreover, they reduce the frequency of COPD exacerbations (6) and offer a potential survival advantage (7). On the contrary, in asthma the safe use of LABA can only be assured if used in combination with an inhaled corticosteroid (ICS) in adequate dosage, preferably in a single inhaler device (8). In fact, by providing effective symptom relief and improvement in lung function, LABAs may mask underlying inflammation that may develop or increase if the dose of ICS is inadequate, leading to more exacerbations and even mortality from uncontrolled asthma, as documented by the Salmeterol Multicenter Asthma Research Trial (SMART) (9).

DOSING STRATEGIES

The large interpatient and interstudy variability in FEV_1 with bronchodilators makes determination of optimum doses difficult. In particular, the low signal-to-noise ratio inherent in the measurement of FEV_1 and the poor precision of the conventional methodologies do not offer a rigorous basis for identification of the minimally effective, optimal, or maximum doses. To overcome this limitation, it has been suggested to use a model-based approach that includes a pooled analysis of study-level data to characterize the bronchodilatory dose response of the examined agent and nonlinear mixed-effects analysis of patient-level data to characterize the effect of baseline covariates (10). However, regulatory authorities do not yet accept model-based approaches (11).

Ideally, β_2-agonists should be used at the lowest dose and frequency required. However, patients with severe COPD need high doses to achieve optimum bronchodilatation (11). High-dose β_2-agonists should also be considered for patients with acute exacerbations of COPD, although there is a great deal of controversy regarding the timing and optimal dose (12). The duration of the bronchodilator effect of inhaled β_2-agonists is decreased in COPD exacerbation (12). To overcome the reduced functional half-life of β_2-agonists, it has been suggested not only to use larger-than-usual doses that are sometimes necessary to relieve airway obstruction but also to shorten the posologic interval (12). However, this therapeutic approach may expose patients to systemic concentrations of the drug that are too high. The treatment of acute asthma includes the repetitive administration of inhaled SABAs, although it has been suggested that high-dose formoterol is well tolerated and provides rapid and effective bronchodilation, similar to high-dose SABAs, and allows less repeated rescue medication (13).

COST-EFFECTIVENESS

Because of differing health policies, costs, health insurance issues, pharmaceutical/commercial aspects, and prescribers' and patients' preferences across different countries worldwide, it is difficult to assess the cost-effectiveness of β_2-agonists. The currently available economic evaluations indicate differences in cost-effectiveness between bronchodilators, but there is a great need to improve the consistency with respect to study methodology and choice of comparator (14). Even taking into account all these limitations, compared with albuterol, the use of formoterol as rescue medication in patients with asthma produces statistically significant improvements in effectiveness, less reliever and maintenance medication use, and reduced healthcare resource use, with no increase or a limited increase in healthcare cost (15). Moreover, an old cost-effectiveness analysis of formoterol versus salmeterol in patients with asthma showed that there was no evidence to suggest that either treatment was more cost effective than the other (16). In COPD, the available economic evidence indicates that salmeterol may be less cost-effective than tiotropium bromide, a long-acting antimuscarinic agent (LAMA), in several specific settings, but there is considerable uncertainty around this finding (17). A recent cost-usefulness analysis of indacaterol in Germany showed that indacaterol 150 μg is better than (lower total costs and better outcomes) tiotropium bromide or salmeterol. An alternative analysis comparing indacaterol 300 μg (maximum dose) against tiotropium showed an incremental cost-effectiveness ratio of approximately €28,300 per quality-adjusted life-year (18).

COMBINATION THERAPY

Combination therapy with an LABA and an ICS is considered an important approach for treating patients with asthma (8) and patients with severe COPD who have frequent exacerbations (19). In patients with asthma who have suboptimal control on low-dose ICS monotherapy, the LABA/ICS combination is a little more effective in reducing the risk of exacerbations requiring oral corticosteroids, improving lung function and symptoms, and decreasing use of rescue β_2-agonists than a higher dose of ICS (20). In adults with asthma who are symptomatic on low to high doses of ICS monotherapy, the addition of an LABA at licensed doses reduces the rate of exacerbations requiring oral steroids, improves lung function and symptoms, and modestly decreases use of rescue β_2-agonists (21). In children, the effects of this treatment option are much more uncertain (21).

In COPD, the addition of LABA to ICS leads to significantly greater improvements in lung function, exacerbations, health status, and breathlessness and a reduction in all-cause mortality compared with monotherapy with the component drugs, although combination treatments may differ with regard to specific outcomes (22). Interestingly, the Toward a Revolution in COPD Health (TORCH) study showed that the mortality benefit is entirely due to the LABA rather than the ICS component (7).

Several studies demonstrate that there are a number of added benefits in using combinations of β_2-agonists and antimuscarinic agents. In particular, LABA/LAMA combination seems to play an important role in maximizing bronchodilation (23). Although improving lung function is a key goal of COPD pharmacotherapy, its measurements alone may not adequately reflect the overall health status of the patient. However, LABA/LAMA combination therapies demonstrate greater improvements in patient-centered outcomes such as dyspnea, symptoms, rescue medication use, and quality of life than individual drugs used alone (24).

MEASURING EFFECTS AND OUTCOMES

In COPD, FEV_1 is used in diagnosis and staging, arterial blood gases are useful in defining respiratory failure, and dynamic hyperinflation helps to explain exertional dyspnea (25). Therefore, to assess the impact of a β_2-agonist in COPD, it is necessary to explore lung function parameters other than FEV_1, for example: FVC and IC to TLC ratio, measures of dyspnea, functional status, health status and HRQoL, exercise tolerance, and breathlessness after exercise (26). The frequency of exacerbations is another important outcome that should be considered in COPD (26). Unfortunately, in contrast to monitoring lung function, there is no gold standard for measuring symptoms such as dyspnea, health status, exercise capacity, physical activity, or exacerbations, because none of the available methods is optimal in all regards (26).

Measuring effects and outcomes of β_2-agonists as monotherapy in asthma is even more complicated. The primary goal of asthma therapy is to achieve and maintain control of disease, as defined by a global assessment of symptoms, reliever use, lung function, and the frequency/severity of exacerbations (8). The impact of β_2-agonists on lung function must always be assessed. However, traditional measures of lung function are an important indicator of severity but insufficient as an index of asthma control (8), and several studies have shown that LABAs might increase the risk of exacerbations and asthma mortality when used by patients with unstable asthma without concomitant ICS or scheduled medical review (9, 27). Therefore, the outcomes of interest of β_2-agonists must include a composite measure incorporating lung function measures, symptom scores, HRQoL measures, and markers that can determine the impact of therapy on underlying inflammation but also asthma death and hospitalization for status asthmaticus.

ADVERSE EFFECTS

All β_2-agonists can induce increased heart rate and palpitations, because some of the β-ARs in the atria and ventricles are β_2, and thus even selective β_2-agonists can provoke direct simulation of the heart (1, 28). Moreover, stimulation of β_2-ARs can result in vasodilation and reflex tachycardia (1, 28).

Administration of β_2-agonists can also induce a transient decrease in Pa_{O_2} despite concomitant bronchodilation. However, the declines observed are small, transient, and have doubtful clinical significance (1, 29).

β-AR stimulation in the liver induces glycogenolysis and raises blood sugar levels (30). Therefore, β_2-agonists should always be used with caution in patients with diabetes because of the risk of ketoacidosis. Hypokalemia is also a risk with β_2-agonist treatment (31) because of stimulation in skeletal muscle of the Na^+, K^+-ATPase-driven pump coupled to β-ARs (1). This increases the ability of the Na^+, K^+ pump to push Na^+ out of the cell and facilitate intracellular accumulation of K^+, thereby lowering plasma levels. Such hypokalemia may precipitate arrhythmias; hence, the use of β_2-agonists is linked to an increased incidence of tachyarrhythmia (1). Dose-related tremor is one of the most characteristic adverse effects after administration of β_2-agonists as they can directly stimulate β-ARs on skeletal muscle (32). An early explanation of the tremor was that β_2-AR shortens the active state of skeletal muscle, which leads to incomplete fusion and reduced tension of tetanic contractions. More recently, tremor has been correlated closely with hypokalemia. Desensitization of β_2-ARs that occurs during the first few days of regular use of β_2-agonist treatment may account for the commonly observed resolution of the majority of these adverse events after the first few doses (1).

Prolonged or repeated use of β_2-agonists leads to loss of some of their effects, a pervasive phenomenon termed tachyphylaxis, refractoriness, or desensitization (1). In effect, regular β_2-agonist use can induce tolerance to their bronchoprotective effects and has the potential to reduce bronchodilator sensitivity to β_2-agonists (33). Tolerance to rescue SABA therapy and increased sensitivity to bronchoconstricting stimuli can lead to decreased asthma control, necessitating hospitalization for further management (34). Tolerance to bronchoprotective effects of LABAs has been demonstrated against spasmogens and exercise, although there is still controversy as to whether LABAs may increase the risk of asthma mortality (35). A study that explored risks of death and asthma outcomes with prescription of LABAs, SABAs, or ICSs in general practice reported no major statistically significant increases in the risks of outcomes with LABAs compared with ICSs in patients with similar exposure characteristics (36). Furthermore, the relative rates of these outcomes did not vary statistically with changes in exposure between LABA and ICS. In fact, the relative rates in heavy long-term users were 1.9 for all-cause mortality and 3.0 for asthma death with SABA; 1.4 and 1.6, respectively, with LABA; and 1.7 and 2.2, respectively, with ICS (36).

It is noteworthy that stepping down treatment with LABAs after the establishment of acceptable asthma control results in the patient's asthma symptoms becoming less well controlled (37). In any case, evidence from randomized clinical trials, meta-analysis of randomized clinical trials, and observational studies, although limited by low statistical power, have indicated that in patients with asthma, the use of combination therapy (LABA plus ICS) is associated with a decreased risk of serious asthma-related events (38). This is particularly true when the concomitant use of LABA plus ICS can be reasonably assured (combined in a single inhaler) (38).

In patients with COPD, the long-term use of β_2-agonists results in sustained improvements in bronchodilatory activity, with no indication of development of tolerance even with the ultra-LABA indacaterol (39). Moreover, a pretreatment with a conventional dose of formoterol or salmeterol does not preclude the ability of inducing a further bronchodilation with albuterol (40).

SAFETY SYSTEMS

Adverse effects of β_2-agonists are greatest when such drugs are administered orally or parenterally (1). The use of inhaled aerosols allows selective treatment of the lungs directly by achieving high drug concentrations in the airway while reducing adverse effects by minimizing systemic drug levels (39). Direct delivery to the lungs also permits a more rapid bronchodilation in response to β_2-agonists.

β_2-Agonists can be administered using pressurized metered-dose inhalers (pMDIs), breath-actuated pMDIs, dry powder inhalers, nebulizers, or soft mist inhalers. Consequently, understanding the possible diverse impact of different modes of administration of β_2-agonists on adverse events is mandatory. The choice of the device used to deliver a β_2-agonist is crucial in determining its pharmacokinetic profile. Increased fine particle mass and lung deposition result in greater systemic exposure, whereas oropharyngeal deposition becomes greater as particle size increases above 6 μm (41). Adverse effects appear to be more common with nebulizer use than with the use of a pMDI, probably because nebulizers deliver a larger systemically absorbed dose (42), whereas deposition of aerosols in the deeper part of the lungs (i.e., the alveolar region) results in an increased proportion of the drug reaching the systemic circulation if delivered doses are not optimized to minimize systemic exposure (43).

Because adverse events with inhaled drugs can be device-dependent, the consequence of a change of the inhalation device should be considered both from an efficacy and a safety standpoint, even when using the same starting dose (32).

GUIDELINES

The strategy document of the Global Initiative for Chronic Obstructive Lung Disease (19) recommends the use of long-acting bronchodilators in all patients with COPD. It does not prefer β_2-agonists to antimuscarinic agents, but it highlights that the choice depends on the availability of medication and the patient's response. Based on efficacy and side effects, inhaled bronchodilators are preferred over oral agents. β_2-Agonists can be combined with antimuscarinic agents if symptoms are not improved with single agents. They can be combined with ICSs if patients with FEV_1 less than 50% of predicted and/or frequent exacerbations are not adequately controlled by long-acting agents, or with the phosphodiesterase-4 inhibitor roflumilast if patients present chronic bronchitis, FEV_1 less than 50% of predicted, and frequent exacerbations that are not adequately controlled by long-acting agents.

In contrast, the Global Initiative for Asthma executive summary (8) recommends never using LABAs as monotherapy for the treatment of subjects with asthma as they may put patients at risk of exacerbations. LABAs are most effective when combined with ICSs, and this combination therapy is the preferred treatment when a medium dose of ICS alone fails to achieve control of asthma. SABAs are the medications of choice for quick relief of bronchospasm during acute exacerbations of asthma and for the pretreatment of exercise-induced bronchoconstriction. They should be used only on an as-needed basis at the lowest dose and frequency required.

FUTURE DEVELOPMENTS

In addition to indacaterol, several once-daily LABAs are currently undergoing development, but detailed information on these drugs is still scarce (1, 44, 45). Olodaterol (BI1744 CL, Boehringer Ingelheim, Ingelheim, Germany) and vilanterol (GSK642444, GlaxoSmithKline, London, UK) are two once-daily LABAs already in phase III clinical trials, whereas abediterol (LAS10097, Almirall, Barcelona, Spain, and Forest Laboratories, New York, NY), AZD3199 (AstraZeneca, Lund, Sweden), and PF-610355 (Pfizer, New York, NY) are in an earlier phase of clinical development; it is likely that the last two agents have been discontinued for strategic and regulatory reasons. Figure 2 shows the chemical structures of these once-daily LABAs. They are single enantiomers of the (R)-configuration. Table 1 illustrates their main pharmacological properties. All have a near full-agonist profile at human β_2-AR. This seems to be an important pharmacological property, because high-efficacy agonists may cause a greater loss of adrenoceptors than low-efficacy agonists but are more tolerant to this, as they have "spare receptors" effect, resulting in a loss in potency but not necessarily any loss of maximal effect and are therefore less sensitive to loss of receptors through desensitization (46).

It is still unclear why LABAs are able to cause such long bronchodilation, and several contrasting hypotheses have been formulated. The debate around the mechanism for the long clinical duration of action exhibited by inhaled LABAs has been ongoing since the discovery and clinical use of salmeterol and formoterol in the early 1990s. Apparently, slow receptor dissociation is not a key factor in the duration of action of inhaled once-daily LABAs, and partitioning of the drug into lipophilic compartments after inhalation is the key determinant of their long duration of action (47). It has been suggested that in ASM, small lipid rafts (50–100 nm), the areas of the plasma membranes where β_2-ARs are held together in close contact with signaling and effectors molecules, might play a role in long duration of action of indacaterol (48). Indacaterol has twofold higher affinity for raft microdomains compared with salmeterol, and this might contribute to the difference in duration of action (48).

Also, vilanterol is a highly lipophilic molecule partitioning into cell membrane and forming depots of drug, but it is not possible to rule out that vilanterol binds directly to an anchored binding site within the β_2-AR (49). On the contrary, olodaterol has a moderate propensity to accumulate in the lipid bilayer, and

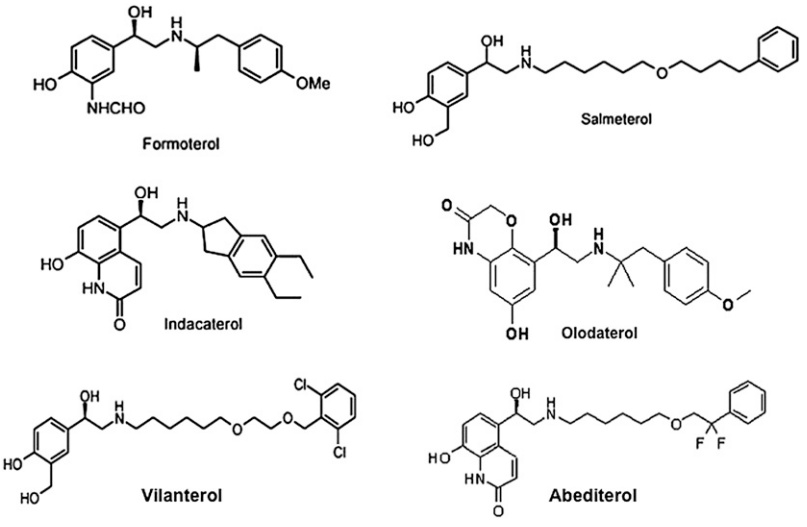

Figure 2. Chemical structures of salmeterol, formoterol, indacaterol, and emerging once-daily long-acting β_2-agonists.

TABLE 1. PHARMACOLOGICAL CHARACTERISTICS OF SEVERAL β_2-AGONISTS

Agonist	pKi		IA (% *Isoprenaline*)	Functional Selectivity Ratio β_1:β_2	Onset $t_{1/2}$ (*min*)	Duration of Action (*min*)	Reference
	β_1	β_2					
Albuterol	5.39 ± 0.06	6.12 ± 0.09	47 ± 1				58
				1:27			49
		6.25 ± 0.04			11.0 ± 4.0	14.6 ± 3.7	60
Salmeterol	6.11 ± 0.09	9.19 ± 0.12	38 ± 1				58
				1:525	19 ± 5	230 ± 55	59
			41 ± 0.01	1:3,000			49
		9.61 ± 0.03		1:1,259			61
	6.14 ± 0.02	9.24 ± 0.08			8.3 ± 0.8	>720	60
Formoterol	6.12 ± 0.09	7.84 ± 0.05	90 ± 1				58
			95 ± 0.04	1:150			49
		8.05 ± 0.02		1:166			61
	6.07 ± 0.04	8.29 ± 0.03	100 ± 3	1:13	6 ± 1	76 ± 14	59
					5.8 ± 0.7	35.3 ± 8.8	60
Indacaterol	6.21 ± 0.12	7.36 ± 0.06	73 ± 1				58
			99 ± 5	1:2	14 ± 1	449 ± 62	59
			86 ± 0.02	1:16			49
		7.92 ± 0.02			7.8 ± 0.7	>720	60
Olodaterol	7.33 ± 0.05	9.14 ± 0.04	88 ± 2	1:65			61
Vilanterol		9.42 ± 0.02	70 ± 3	1:2,400	3.1 ± 0.3		49

Definition of abbreviations: IA = intrinsic activity; pKi = the negative logarithm to base 10 of the equilibrium dissociation constant of a ligand determined in inhibition studies.

therefore the microkinetic theory cannot be dismissed fully (50). Moreover, a second aspect, namely, the tight binding of olodaterol to the human β_2-AR and formation of the ternary complex, was identified. It has been suggested that this complex, with a dissociation half-life of 18 hours, indeed might be a rationale for the 24-h duration of action of olodaterol (50), but this contrasts with the view that slow receptor dissociation is not a key factor in the duration of action of inhaled once-daily LABAs (47).

However, regardless of the mechanism that explains its duration of action, olodaterol induces bronchodilation up to 24 hours postdosing in patients with COPD (51) and protects against methacholine-induced bronchoconstriction for up to 32 hours after the administration of a single dose in patients with intermittent asthma (52), with a clear dose–response relationship.

Vilanterol produces a dose-dependent rapid bronchodilation in patients with COPD, which is maintained over 24 hours after chronic administration, with a safety and tolerability profile similar to placebo (53). It results in prolonged bronchodilation of at least 24 hours with good tolerability in patients with asthma receiving ICSs (54), and evidence suggests no advantage over a 24-hour period of vilanterol twice daily versus once-daily dosing for the same total daily dose (55).

Abediterol elicits rapid bronchodilation (5 min after dosing) that is faster and longer lasting than salmeterol 50 μg twice daily (45).

Fixed-dose combination formulations containing a novel once-daily LABA with LAMA are being developed by a number of companies. Indacaterol/glycopyrronium bromide (QVA149, Novartis, Basel, Switzerland), olodaterol/tiotropium bromide (Boehringer Ingelheim), and vilanterol/umeclidinium bromide (GlaxoSmithKline) are in advanced development for the treatment of COPD and demonstrate significant broncholytic effects (1, 2, 44). Other companies are combining formoterol with aclidinium or glycopyrronium, but these combinations have 12-hour duration of action (45).

Fixed dose combinations of novel ultra-LABAs and ICSs are also under development, including vilanterol/fluticasone furoate (GlaxoSmithKline), which is in phase III clinical trials that involve both patients with asthma and patients with COPD. It has a good safety and tolerability profile and improves lung function compared with placebo in patients with COPD (56) and provides significant bronchoprotection against the early asthmatic response at the trough of dosing (i.e., 23 h post last dose) in subjects with mild asthma (57). Indacaterol/mometasone (QMF149, Novartis) is in phase II clinical trials, although limited clinical data are available (45).

Author disclosures are available with the text of this article at www.atsjournals.org.

References

1. Cazzola M, Page CP, Calzetta L, Matera MG. Pharmacology and therapeutics of bronchodilators. *Pharmacol Rev* 2012;64:450–504.
2. Cazzola M, Calzetta L, Matera MG. β_2-adrenoceptor agonists: current and future direction. *Br J Pharmacol* 2011;163:4–17.
3. Billington CK, Ojo OO, Penn RB, Ito S. cAMP regulation of airway smooth muscle function. *Pulm Pharmacol Ther* 2013;26:112–120.
4. Billington CK, Hall IP. Novel cAMP signalling paradigms: therapeutic implications for airway disease. *Br J Pharmacol* 2012;166:401–410.
5. Cazzola M, Testi R, Matera MG. Clinical pharmacokinetics of salmeterol. *Clin Pharmacokinet* 2002;41:19–30.
6. Wang J, Nie B, Xiong W, Xu Y. Effect of long-acting beta-agonists on the frequency of COPD exacerbations: a meta-analysis. *J Clin Pharm Ther* 2012;37:204–211.
7. Suissa S, Ernst P, Vandemheen KL, Aaron SD. Methodological issues in therapeutic trials of COPD. *Eur Respir J* 2008;31:927–933.
8. Bateman ED, Hurd SS, Barnes PJ, Bousquet J, Drazen JM, FitzGerald M, Gibson P, Ohta K, O'Byrne P, Pedersen SE, *et al.* Global strategy for asthma management and prevention: GINA executive summary. *Eur Respir J* 2008;31:143–178.
9. Nelson HS, Weiss ST, Bleecker ER, Yancey SW, Dorinsky PM. The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. *Chest* 2006;129:15–26.
10. Renard D, Looby M, Kramer B, Lawrence D, Morris D, Stanski DR. Characterization of the bronchodilatory dose response to indacaterol in patients with chronic obstructive pulmonary disease using model-based approaches. *Respir Res* 2011;12:54.
11. Martinez FJ, Donohue JF, Rennard SI. The future of chronic obstructive pulmonary disease treatment–difficulties of and barriers to drug development. *Lancet* 2011;378:1027–1037.
12. Cazzola M, Matera MG. Long-acting β_2-agonists as potential option in the treatment of acute exacerbations of COPD. *Pulm Pharmacol Ther* 2003;16:197–201.
13. Rodrigo GJ, Neffen H, Colodenco FD, Castro-Rodriguez JA. Formoterol for acute asthma in the emergency department: a systematic review with meta-analysis. *Ann Allergy Asthma Immunol* 2010;104:247–252.

14. Lindgren B, Sears MR, Campbell M, Villasante C, Huang S, Lindh A, Petermann W, Svensson K, Berggren F, Pauwels RA. Cost-effectiveness of formoterol and salbutamol as asthma reliever medication in Sweden and in Spain. *Int J Clin Pract* 2005;59:62–68.
15. Rutten-van Mölken MP, van Doorslaer EK, Till MD. Cost-effectiveness analysis of formoterol versus salmeterol in patients with asthma. *Pharmacoeconomics* 1998;14:671–684.
16. Chong J, Karner C, Poole P. Tiotropium versus long-acting beta-agonists for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2012;9:CD009157.
17. Price D, Gray A, Gale R, Asukai Y, Mungapen L, Lloyd A, Peters L, Neidhardt K, Gantner T. Cost-utility analysis of indacaterol in Germany: a once-daily maintenance bronchodilator for patients with COPD. *Respir Med* 2011;105:1635–1647.
18. Rutten-van Mölken MP, Goossens LM. Cost effectiveness of pharmacological maintenance treatment for chronic obstructive pulmonary disease: a review of the evidence and methodological issues. *Pharmacoeconomics* 2012;30:271–302.
19. Vestbo J, Hurd SS, Agusti AG, Jones PW, Vogelmeier C, Anzueto A, Barnes PJ, Fabbri LM, Martinez FJ, Nishimura M, *et al*. Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease, GOLD Executive Summary. *Am J Respir Crit Care Med* 2013;187:347–365.
20. Ducharme FM, Ni Chroinin M, Greenstone I, Lasserson TJ. Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma. *Cochrane Database Syst Rev* 2010;4:CD005533.
21. Ducharme FM, Ni Chroinin M, Greenstone I, Lasserson TJ. Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children. *Cochrane Database Syst Rev* 2010;4:CD005535.
22. Hanania NA. The impact of inhaled corticosteroid and long-acting β_2-agonist combination therapy on outcomes in COPD. *Pulm Pharmacol Ther* 2008;21:540–550.
23. Cazzola M, Molimard M. The scientific rationale for combining long-acting β_2-agonists and muscarinic antagonists in COPD. *Pulm Pharmacol Ther* 2010;23:257–267.
24. van der Molen T, Cazzola M. Beyond lung function in COPD management: effectiveness of LABA/LAMA combination therapy on patient-centred outcomes. *Prim Care Respir J* 2012;21:101–108.
25. ZuWallack RL, Haggerty MC, Jones P. Clinically meaningful outcomes in patients with chronic obstructive pulmonary disease. *Am J Med* 2004;117:49S–59S.
26. Cazzola M, MacNee W, Martinez FJ, Rabe KF, Franciosi LG, Barnes PJ, Brusasco V, Burge PS, Calverley PMA, Celli BR, *et al*. Outcomes for COPD pharmacological trials: from lung function to biomarkers. *Eur Respir J* 2008;31:416–469.
27. Beasley R, Perrin K, Weatherall M, Wijesinghe M. Call for withdrawal of LABA single-therapy inhaler in asthma. *Lancet* 2010;376:750–751.
28. Cazzola M, Matera MG, Donner CF. Inhaled β_2-adrenoceptor agonists: cardiovascular safety in patients with obstructive lung disease. *Drugs* 2005;65:1595–1610.
29. Cazzola M, Noschese P, De Michele F, D'Amato G, Matera MG. Effect of formoterol/budesonide combination on arterial blood gases in patients with acute exacerbation of COPD. *Respir Med* 2006;100:212–217.
30. Philipson LH. β-Agonists and metabolism. *J Allergy Clin Immunol* 2002; 110:S313–S317.
31. Scheinin M, Koulu M, Laurikainen E, Allonen H. Hypokalaemia and other non-bronchial effects of inhaled fenoterol and salbutamol: a placebo-controlled dose–response study in healthy volunteers. *Br J Clin Pharmacol* 1987;24:645–653.
32. Cazzola M, Matera MG. Tremor and β_2-adrenergic agents: is it a real clinical problem? *Pulm Pharmacol Ther* 2012;25:4–10.
33. Cheung D, Timmers MC, Zwinderman AH, Bel EH, Dijkman JH, Sterk PJ. Long-term effects of a long-acting β_2-adrenoceptor agonist, salmeterol, on airway hyperresponsivenessin patients with mild asthma. *N Engl J Med* 1992;327:1198–1203.
34. Liao MM, Ginde AA, Clark S, Camargo CA Jr. Salmeterol use and risk of hospitalization among emergency department patients with acute asthma. *Ann Allergy Asthma Immunol* 2010;104:478–484.
35. Weatherall M, Wijesinghe M, Perrin K, Beasley R. Long-acting beta-agonists and asthma death: how useful are different study designs to evaluate the potential association? *J Asthma* 2010;47:434–438.
36. de Vries F, Setakis E, Zhang B, van Staa TP. Long-acting β_2-agonists in adult asthma and the pattern of risk of death and severe asthma outcomes: a study using the GPRD. *Eur Respir J* 2010;36:494–502.
37. Thomas A, Lemanske RF, Jackson DJ. Approaches to stepping up and stepping down care in asthmatic patients. *J Allergy Clin Immunol* 2011;128:915–924.
38. Rodrigo GJ, Castro-Rodríguez JA. Safety of long-acting β agonists for the treatment of asthma: clearing the air. *Thorax* 2012;67:342–349.
39. Chapman KR, Rennard SI, Dogra A, Owen R, Lassen C, Kramer B. Long-term safety and efficacy of indacaterol, a long-acting β_2-agonist, in subjects with COPD: a randomized, placebo-controlled study. *Chest* 2011;140:68–75.
40. Cazzola M, Di Perna F, Noschese P, Vinciguerra A, Calderaro F, Girbino G, Matera MG. Effects of formoterol, salmeterol or oxitropium bromide on airway responses to salbutamol in COPD. *Eur Respir J* 1998;11:1337–1341.
41. Dolovich MB, Dhand R. Aerosol drug delivery: developments in device design and clinical use. *Lancet* 2011;377:1032–1045.
42. Dolovich MB, Ahrens RC, Hess DR, Anderson P, Dhand R, Rau JL, Smaldone GC, Guyatt G. Device selection and outcomes of aerosol therapy: evidence-based guidelines: American College of Chest Physicians/ American College of Asthma, Allergy, and Immunology. *Chest* 2005;127: 335–371.
43. Usmani OS, Biddiscombe MF, Barnes PJ. Regional lung deposition and bronchodilator response as a function of β_2-agonist particle size. *Am J Respir Crit Care Med* 2005;172:1497–1504.
44. Matera MG, Page CP, Cazzola M. Novel bronchodilators for the treatment of chronic obstructive pulmonary disease. *Trends Pharmacol Sci* 2011;32:495–506.
45. Cazzola M, Rogliani P, Segreti A, Matera MG. An update on bronchodilators in Phase I and II clinical trials. *Expert Opin Investig Drugs* 2012;21:1489–1501.
46. Charlton SJ. Agonist efficacy and receptor desensitization: from partial truths to a fuller picture. *Br J Pharmacol* 2009;158:165–168.
47. Sykes DA, Charlton SJ. Slow receptor dissociation is not a key factor in the duration of action of inhaled long-acting β_2-adrenoceptor agonists. *Br J Pharmacol* 2012;165:2672–2683.
48. Lombardi D, Cuenoud B, Krämer SD. Lipid membrane interactions of indacaterol and salmeterol: do they influence their pharmacological properties? *Eur J Pharm Sci* 2009;38:533–547.
49. Slack RJ, Barrett VJ, Morrison VS, Sturton RG, Emmons AJ, Ford AJ, Knowles RG. In vitro pharmacological characterization of vilanterol, a novel long acting β_2-adrenoceptor agonist with 24 hour duration of action. *J Pharmacol Exp Ther* 2013;344:218–230.
50. Casarosa P, Kollak I, Kiechle T, Ostermann A, Schnapp A, Kiesling R, Pieper M, Sieger P, Gantner F. Functional and biochemical rationales for the 24-hour-long duration of action of olodaterol. *J Pharmacol Exp Ther* 2011;337:600–609.
51. van Noord JA, Smeets JJ, Drenth BM, Rascher J, Pivovarova A, Hamilton AL, Cornelissen PJ. 24-hour bronchodilation following a single dose of the novel β_2-agonist olodaterol in COPD. *Pulm Pharmacol Ther* 2011;24:666–672.
52. O'Byrne PM, van der Linde J, Cockcroft DW, Gauvreau GM, Brannan JD, Fitzgerald M, Watson RM, Milot J, Davis B, O'Connor M, *et al*. Prolonged bronchoprotection against inhaled methacholine by inhaled BI 1744, a long-acting β_2-agonist, in patients with mild asthma. *J Allergy Clin Immunol* 2009;124:1217–1221.
53. Hanania NA, Feldman G, Zachgo W, Shim JJ, Crim C, Sanford L, Lettis S, Barnhart F, Haumann B. The efficacy and safety of the novel long-acting β_2 agonist vilanterol in COPD patients: a randomized placebo-controlled trial. *Chest* 2012;142:119–127.
54. Lötvall J, Bateman ED, Bleecker ER, Busse WW, Woodcock A, Follows R, Lim J, Stone S, Jacques L, Haumann B. 24-h duration of the novel LABA vilanterol trifenatate in asthma patients treated with inhaled corticosteroids. *Eur Respir J* 2012;40:570–579.
55. Sterling R, Lim J, Frith L, Snowise NG, Jacques L, Haumann B. Efficacy and optimal dosing interval of the long-acting beta$_2$ agonist, vilanterol, in persistent asthma: a randomised trial. *Respir Med* 2012;106:1110–1115.

56. Lötvall J, Bakke PS, Bjermer L, Steinshamn S, Scott-Wilson C, Crim C, Sanford L, Haumann B. Efficacy and safety of 4 weeks' treatment with combined fluticasone furoate/vilanterol in a single inhaler given once daily in COPD: a placebo-controlled randomised trial. *BMJ Open* 2012;2:e000370.
57. Oliver A, Quinn D, Goldfrad C, van Hecke B, Ayer J, Boyce M. Combined fluticasone furoate/vilanterol reduces decline in lung function following inhaled allergen 23 h after dosing in adult asthma: a randomised, controlled trial. *Clin Transl Allergy* 2012;2:11.
58. Battram C, Charlton SJ, Cuenoud B, Dowling MR, Fairhurst RA, Farr D, Fozard JR, Leighton-Davies JR, Lewis CA, McEvoy L, *et al*. In vitro and in vivo pharmacological characterization of 5-[(R)-2-(5,6-diethyl-indan-2-ylamino)-1-hydroxy-ethyl]-8-hydroxy-1H-quinolin-2-one (indacaterol), a novel inhaled β_2 adrenoceptor agonist with a 24-h duration of action. *J Pharmacol Exp Ther* 2006;317:762–770.
59. Aparici M, Gómez-Angelats M, Vilella D, Otal R, Carcasona C, Viñals M, Ramos I, Gavaldà A, De Alba J, Gras J, *et al*. Pharmacological characterization of abediterol, a novel inhaled β_2-adrenoceptor agonist with long duration of action and a favorable safety profile in preclinical models. *J Pharmacol Exp Ther* 2012;342:497–509.
60. Naline E, Trifilieff A, Fairhurst RA, Advenier C, Molimard M. Effect of indacaterol, a novel long-acting β_2-agonist, on isolated human bronchi. *Eur Respir J* 2007;29:575–581.
61. Bouyssou T, Casarosa P, Naline E, Pestel S, Konetzki I, Devillier P, Schnapp A. Pharmacological characterization of olodaterol, a novel inhaled β_2-adrenoceptor agonist exerting a 24-hour-long duration of action in preclinical models. *J Pharmacol Exp Ther* 2010;334:53–62.